



Selenoprotein Gene Nomenclature

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Selenoprotein Gene Nomenclature*

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Vadim N. Gladyshev,^{a,b1} Elias S. Arnér,^c Marla J. Berry,^d Regina Brigelius-Flohé,^e Elspeth A. Bruford,^f Raymond F. Burk,^g Bradley A. Carlson,^h Sergi Castellano,ⁱ Laurent Chavatte,^j Marcus Conrad,^k Paul R. Copeland,^l Alan M. Diamond,^m Donna M. Driscoll,ⁿ Ana Ferreira,^{o,p} Leopold Flohé,^{q,r} Fiona R. Green,^s Roderic Guigó,^{t,u} Diane E. Handy,^v Dolph L. Hatfield,^h John Hesketh,^{w,x,y} Peter R. Hoffmann,^d Arne Holmgren,^c Robert J. Hondal,^z Michael T. Howard,^{aa} Kaixun Huang,^{bb} Hwa-Young Kim,^{cc} Ick Young Kim,^{dd} Josef Köhrle,^{ee} Alain Krol,^{ff} Gregory V. Kryukov,^{gg} Byeong Jae Lee,^{hh} Byung Cheon Lee,^{dd} Xin Gen Lei,ⁱⁱ Qiong Liu,^{jj} Alain Lescure,^{ff,kk} Alexei V. Lobanov,^a Joseph Loscalzo,^{ll} Matilde Maiorino,^f Marco Mariotti,^a K. Sandeep Prabhu,^{mm} Margaret P. Rayman,ⁿⁿ Sharon Rozovsky,^{oo} Gustavo Salinas,^{pp} Edward E. Schmidt,^{qq} Lutz Schomburg,^{ee} Ulrich Schweizer,^{rr} Miljan Simonović,^{ss} Roger A. Sunde,^{tt} Petra A. Tsuji,^{uu} Susan Tweedie,^f Fulvio Ursini,^r Philip D. Whanger,^{vv} and Yan Zhang^{jj}

From the ^aDepartment of Medicine, Division of Genetics, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, the ^bBroad Institute of Harvard and MIT, Cambridge, Massachusetts 02142, the ^cDepartment of Medical Biochemistry and Biophysics (MBB), Division of Biochemistry, Karolinska Institutet, SE-171 77, Stockholm, Sweden, the ^dDepartment of Cell and Molecular Biology, John A. Burns School of Medicine, University of Hawaii at Manoa, Honolulu, Hawaii 96813, the ^eGerman Institute of Human Nutrition Potsdam-Rehbruecke, 14558 Nuthetal, Germany, the ^fHUGO Gene Nomenclature Committee (HGNC), European Bioinformatics Institute-European Molecular Biology Laboratory (EMBL-EBI), Hinxton CB10 1SD, United Kingdom, the ^gDepartment of Medicine, Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University School of Medicine, Nashville, Tennessee 37232, the ^hMolecular Biology of Selenium Section, Mouse Cancer Genetics Program, Center for Cancer Research, National Institutes of Health, Bethesda, Maryland 20892, the ⁱDepartment of Evolutionary Genetics, Max Planck Institute for Evolutionary Anthropology, 04103 Leipzig, Germany, the ^jCentre International de Recherche en Infectiologie, CIRI, INSERM U1111, and CNRS/ENS UMR5308, 69007 Lyon, France, the ^kHelmholtz Zentrum München, Institute of Developmental Genetics, 85764 Neuherberg, Germany, the ^lDepartment of Biochemistry and Molecular Biology, Rutgers-Robert Wood Johnson Medical School, Piscataway, New Jersey 08854, the ^mDepartment of Pathology, University of Illinois at Chicago, Chicago, Illinois 60607, the ⁿDepartment of Cellular and Molecular Medicine, Lerner Research Institute, Cleveland Clinic Foundation, Cleveland, Ohio 44195, the ^oPathophysiology of Striated Muscles Laboratory, Unit of Functional and Adaptive Biology (BFA), University Paris Diderot, Sorbonne Paris Cité, BFA, UMR CNRS 8251, 75250 Paris, France, the ^pAP-HP, Centre de Référence Maladies Neuromusculaires Paris-Est, Groupe Hospitalier Pitié-Salpêtrière, 75013 Paris, France, the ^qUniversidad de la República, Facultad de Medicina, Departamento de Bioquímica, 11800 Montevideo, Uruguay, the ^rDepartment of Molecular Medicine, University of Padova, I-35121 Padova, Italy, the ^sDivision of Cardiovascular Sciences, School of Medical Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester, United Kingdom, the ^tCentre for Genomic Regulation (CRG), 08003 Barcelona, Spain, the ^uUniversitat Pompeu Fabra (UPF), 08002 Barcelona, Spain, the ^vDepartment of Medicine, Cardiovascular Division, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts 02115, the ^wInstitute for Cell and Molecular Biosciences, Newcastle University, Newcastle-upon-Tyne NE1 7RU, United Kingdom, the ^xHuman Nutrition Research Centre, Newcastle University, Newcastle-upon-Tyne NE1 7RU, United Kingdom, the ^yThe Medical School, Newcastle University, Newcastle-upon-Tyne NE2 4HH, United Kingdom, the ^zDepartment of Biochemistry, University of Vermont, Burlington, Vermont 05405, the ^{aa}Department of Human Genetics, University of Utah, Salt Lake City, Utah 84112, the ^{bb}Hubei Key Laboratory of Bioinorganic Chemistry & Materia Medica, School of Chemistry and Chemical Engineering, Huazhong University of Science and Technology, Wuhan 430074, Peoples Republic of China, the ^{cc}Department of Biochemistry and Molecular Biology, Yeungnam University College of Medicine, Daegu 42415, South Korea, the ^{dd}College of Life Sciences and Biotechnology, Korea University, Seoul 02841, South Korea, the ^{ee}Institute for Experimental Endocrinology, Charité-Universitätsmedizin Berlin, D-13353 Berlin, Germany, the ^{ff}Architecture et Réactivité de l'ARN, Université de Strasbourg, Centre National de la Recherche Scientifique, Institut de Biologie Moléculaire et Cellulaire, 67084 Strasbourg, France, the ^{gg}KSQ Therapeutics, Cambridge, Massachusetts 02139, the ^{hh}School of Biological Sciences, Seoul National University, Seoul 151-742, South Korea, the ⁱⁱDepartment of Animal Science, Cornell University, Ithaca, New York 14853, the ^{jj}Shenzhen Key Laboratory of Marine Biotechnology and Ecology, College of Life Science, Shenzhen University, Shenzhen, 518060, Guangdong Province, Peoples Republic of China, the ^{kk}Centre National de la Recherche Scientifique, 75794 Paris, France, the ^{ll}Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, the ^{mm}Department of Veterinary and Biomedical Sciences, The Pennsylvania State University, University Park, Pennsylvania 16802, the ⁿⁿDepartment of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford GU2 7XH, United Kingdom, the ^{oo}Department of Chemistry and Biochemistry, University of Delaware, Newark, Delaware 19716, the ^{pp}Cátedra de Inmunología, Facultad de Química, Instituto de Higiene, CP11600 Montevideo, Uruguay, the ^{qq}Department of Microbiology and Immunology, Montana State University, Bozeman, Montana 59717, the ^{rr}Rheinische Friedrich-Wilhelms Universität Bonn, Institut für Biochemie und Molekularbiologie, 53115 Bonn, Germany, the ^{ss}Department of Biochemistry and Molecular Genetics, University of Illinois at Chicago, Chicago, Illinois 60607, the ^{tt}Department of Nutritional Sciences, University of Wisconsin, Madison, Wisconsin 53706, the ^{uu}Department of Biological Sciences, Towson University, Towson, Maryland 21252, and the ^{vv}Department of Environmental and Molecular Toxicology, College of Agricultural Sciences, Oregon State University, Corvallis, Oregon 97331

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The human genome contains 25 genes coding for selenocysteine-containing proteins (selenoproteins). These proteins are involved in a variety of functions, most notably redox homeostasis. Selenoprotein enzymes with known functions are designated according to these functions: TXNRD1, TXNRD2, and TXNRD3 (thioredoxin reductases), GPX1, GPX2, GPX3, GPX4, and GPX6 (glutathione peroxidases), DIO1, DIO2, and DIO3 (iodothyronine deiodinases), MSRB1 (methionine sulfoxide reductase B1), and SEPHS2 (selenophosphate synthetase 2). Selenoproteins without known functions have traditionally been denoted by SEL or SEP symbols. However, these symbols are sometimes ambiguous and conflict with the approved nomenclature for several other genes. Therefore, there is a need to implement a rational and coherent nomenclature system for selenoprotein-encoding genes. Our solution is to use the root symbol SELENO followed by a letter. This nomenclature applies to SELENOF (selenoprotein F, the 15-kDa selenoprotein, SEP15), SELENOH (selenoprotein H, SELH, C11orf31), SELENOI (selenoprotein I, SELI, EPT1), SELENOK (selenoprotein K, SELK), SELENOM (selenoprotein M, SELM), SELENON (selenoprotein N, SEPNI, SELN), SELENOO (selenoprotein O, SELO), SELENOP (selenoprotein P, SeP, SEPP1, SELP), SELENOS (selenoprotein S, SELS, SEPS1, VIMP), SELENOT (selenoprotein T, SELT), SELENOV (selenoprotein V, SELV), and SELENOW (selenoprotein W, SELW, SEPW1). This system, approved by the HUGO Gene Nomenclature Committee, also resolves conflicting, missing, and ambiguous designations for selenoprotein genes and is applicable to selenoproteins across vertebrates.

Selenium is an essential trace element in humans, which is present in proteins in the form of the 21st proteinogenic amino acid, selenocysteine (Sec).² Sec is co-translationally inserted into a polypeptide chain in response to in-frame UGA codons directed by the Sec insertion sequence element, a stem-loop structure in the 3'-UTRs of selenoprotein mRNAs. The human genome contains 25 selenoprotein genes (1), and selenoproteins are essential for embryo development and human health (2, 3). Among the selenoproteins, 13 have known functions; at least 12 of them serve as oxidoreductases, wherein Sec is the catalytic redox-active residue. The redox theme is also common for selenoproteins in other organisms (4).

The remaining 12 selenoproteins either have no known function, or their functions are only partially established. One of the selenoproteins, selenoprotein P (5), requires special mention as

it has more than one Sec. It is a major plasma selenoprotein that delivers selenium primarily from the liver to other organs (6, 7), and is involved in selenium transport and metabolism within organs. However, this protein also has an N-terminal Sec-containing thioredoxin domain similar to that found in most selenoproteins with known functions, which points to a potential redox function. Several other selenoproteins, including selenoproteins H, M, T, V, W, and Sep15, also possess thioredoxin-like domains, suggesting redox-related functions (8).

Selenoproteins are not all homologous, but are characterized by their incorporation of Sec. Historically they have been given designations by the groups that discovered them, e.g. because of its presence in plasma the respective selenoprotein was named selenoprotein P (9, 10), or because of its size another protein was called the 15-kDa selenoprotein or Sep15 (11). However, some selenoproteins were identified independently by two or more groups, which created confusion and discrepancies in the field. For example, the same protein was named selenoprotein R by one group (12), but discovered concurrently and designated by another group as selenoprotein X (13). This protein was then functionally characterized (14) and renamed MsrB1 (for methionine-*R*-sulfoxide reductase 1) (15), but all three designations persist in the literature and/or databases. Another problematic example is the nomenclature used for thioredoxin reductases. The names for the first thioredoxin reductase, which had been known decades before its selenoprotein nature was discovered (16), are generally internally consistent, although they differ in the abbreviations used, e.g. TR1 and TrxR1 (17). The second and third thioredoxin reductases discovered, however, were named inconsistently by the authors, wherein the mitochondrial thioredoxin reductase was designated as TrxR2 (18) and TR3 (19), and the testis-specific thioredoxin-glutathione reductase has been alternatively labeled as TR2 (19), TrxR3, or TGR.

Designations are also confusing for several other selenoproteins. For example, selenoprotein S was named Sels (1), but a later paper introduced the designation VIMP (20). Similarly, selenoprotein H was named SelH (1), but also C11orf31, and selenoprotein I was named SelI (1), but also called EPT1 (21). To avoid confusion, and at the instigation of the HUGO Gene Nomenclature Committee (HGNC), we describe a new standardized designation system for human (and other vertebrate) selenoproteins.

Results and Discussion

Resolving the Nomenclature of Selenoprotein Genes—Human gene designations are approved by the HUGO Gene Nomenclature Committee (HGNC), and genes in other mammals follow the same designations. Selenoproteins have traditionally been published using SEL or SEP symbols followed by a letter or a number. Unfortunately, for naming the genes encoding these proteins, the SEL root was not an option as it was already approved for the selectin gene family; for example, *SELP* is the approved gene symbol for selectin P (P-selectin) and not selenoprotein P. Some selenoprotein genes had been approved using the root SEP (i.e. *SEPNI*, *SEPP1*, and *SEPW1*) but this could not be utilized for all selenoproteins as selenoprotein T gene would then be *SEPT* or *SEPT1*, and *SEPT#* is already used

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¹ To whom correspondence should be addressed. E-mail: vgladyshv@rics.bwh.harvard.edu.

² The abbreviations used are: Sec, selenocysteine; TXNRD, thioredoxin reductases; GPX, glutathione peroxidase; DIO, iodothyronine deiodinase; SEPHS2, selenophosphate synthetase 2; SELENOF, 15-kDa selenoprotein; SELENOH, selenoprotein H; SELENOI, selenoprotein I; SELENOK, selenoprotein K; SELENOM, selenoprotein M; SELENON, selenoprotein N; SELENOO, selenoprotein O; SELENOP, selenoprotein P; SELENOS, selenoprotein S; SELENOT, selenoprotein T; SELENOV, selenoprotein V; SELENOW, selenoprotein W; HGNC, HUGO Gene Nomenclature Committee.

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for the septin genes. HGNC does not use the same root for unrelated groups of genes (*e.g.* SEL for selectins and selenoproteins) and does not endorse the use of multiple root symbols for genes sharing a common name (*e.g.* SEP and SEL for selenoprotein). With a view to solving these issues, HGNC approached selenoprotein researchers to propose a new unifying root symbol for all selenoprotein genes.

Proposal for a New Nomenclature—We propose that all selenoproteins (except those that have been functionally characterized, *e.g.* with enzymatic activity) use the root symbol SELENO followed by a letter. This gene nomenclature is designed to highlight selenium, the key functional site in these proteins, and to provide a new and unambiguous root for these genes. The new nomenclature applies to 12 human selenoprotein genes as detailed in Table 1. Selenoproteins with known functions will continue to use the same designations (Table 2). Once functions are established for other selenoproteins, they may be renamed, as required. The proposed designations apply to the selenoprotein genes; although the same designations may be used for many of the encoded proteins, traditional names of selenoproteins, *e.g.* selenoprotein P, may also be used.

Selenoprotein Gene Designation in Other Species—The new HGNC nomenclature will automatically be used to designate orthologous selenoprotein genes in other vertebrates and extended to accommodate selenoprotein genes with no orthologs in human (22) (Table 3). Where vertebrate gene

duplications have occurred, the additional paralogs will be named in line with the human genes, but with suffixes on the symbols, *e.g.* zebrafish selenot1a, selenot1b, and selenot2. Selenoproteins are widespread in all three domains of life. Despite the fact that land plants, yeast, and some other species have lost selenoprotein biosynthesis pathways, a unifying nomenclature beyond vertebrates might be desirable. We suggest using the human nomenclature described in this paper for orthologs of vertebrate selenoprotein genes. This nomenclature may also be extended to accommodate additional selenoprotein genes as they are discovered. Although we use human designations in this paper, we note that most vertebrates use all uppercase letters for genes and proteins (italics for genes), rodents use title case for genes (uppercase for proteins), *Xenopus* and zebrafish use lowercase for genes and title case for proteins, and Anolis use lowercase for genes and uppercase for proteins.

Designations of Proteins That Do Not Contain Selenocysteine—There exists another class of selenium-containing proteins, those which contain a bound atom of selenium but do not contain a UGA-encoded Sec, for which there is also ambiguous nomenclature. For example, selenium-binding protein 1 (SBP1), also referred to as SELENBP1 or hSP56, is one such protein (23). The naming of such proteins will not be included in the new nomenclature as they lack Sec. Similarly, the machinery for Sec biosynthesis and insertion will not be renamed.

Implementation—The new selenoprotein gene nomenclature has been approved by the HGNC, can be found on their website (<http://www.genenames.org/cgi-bin/genefamilies/set/890>), and will be found in all major genomic resources in due course. We recommend that future publications primarily use

TABLE 1

Selenoprotein genes using the new SELENO root

New HGNC selenoprotein gene nomenclature is indicated in the column "symbol." Previous HGNC symbols (shown with *) will become synonyms, along with other previously used designations.

| Symbol | Name | Synonyms | Refs. |
|----------|-----------------|-------------------------|-------|
| SELENOF | Selenoprotein F | Selenoprotein 15, SEP15 | 11 |
| SELENOH | Selenoprotein H | SELH, C11orf31* | 1 |
| SELENOI | Selenoprotein I | SELI, EPT1* | 1, 21 |
| SELENOK | Selenoprotein K | SELK | 1 |
| SELENO M | Selenoprotein M | SELM, SEPM | 25 |
| SELENO N | Selenoprotein N | SEPN1*, SELN | 13 |
| SELENO O | Selenoprotein O | SELO | 1 |
| SELENO P | Selenoprotein P | SEPP1*, SeP, SELP, SEPP | 26 |
| SELENO S | Selenoprotein S | SELS, SEPS1, VIMP* | 1 |
| SELENO T | Selenoprotein T | SELT | 12 |
| SELENO V | Selenoprotein V | SELV | 1 |
| SELENO W | Selenoprotein W | SELW, SEPW1* | 27 |

TABLE 2

Selenoprotein genes named based on encoded enzymatic activity

Note that the nomenclature of these genes will not be changing to use the SELENO root.

| Symbol | Name | Synonyms | Refs. |
|--------|-----------------------------------|--|------------|
| TXNRD1 | Thioredoxin reductase 1 | TR1, TRXR1 | 16, 28, 29 |
| TXNRD2 | Thioredoxin reductase 2 | TRXR2, TR3, mitochondrial thioredoxin reductase | 18, 19 |
| TXNRD3 | Thioredoxin-glutathione reductase | TGR, TRXR3, TR2 | 19 |
| GPX1 | Glutathione peroxidase 1 | Cytosolic glutathione peroxidase, GSHPX1 | 30–35 |
| GPX2 | Glutathione peroxidase 2 | GSHPX-GI | 36 |
| GPX3 | Glutathione peroxidase 3 | Plasma glutathione peroxidase | 37 |
| GPX4 | Glutathione peroxidase 4 | Phospholipid hydroperoxide glutathione peroxidase, PHGPX | 38, 39 |
| GPX6 | Glutathione peroxidase 6 | | |
| DIO1 | Iodothyronine deiodinase 1 | D1 | 40, 41 |
| DIO2 | Iodothyronine deiodinase 2 | D2 | 42 |
| DIO3 | Iodothyronine deiodinase 3 | D3 | 43 |
| MSRB1 | Methionine sulfoxide reductase B1 | SELR, SELX, SEPX1 | 12–14 |
| SEPHS2 | Selenophosphate synthetase 2 | SPS2 | 44 |

TABLE 3

Vertebrate selenoprotein genes absent in human and mouse

New selenoprotein gene nomenclature is indicated in the column "symbol."

| Symbol | Name | Synonyms | Refs. |
|-----------|--|--------------|--------|
| SELENO J | Selenoprotein J | SELJ | 45 |
| SELENO U | Selenoprotein U | SELU | 46 |
| SELENO L | Selenoprotein L | SELL | 47 |
| SELENO E | Selenoprotein E, fish selenoprotein 15 | FEP15 | 48 |
| SELENO P2 | Selenoprotein P2 | SEPP2, SELPb | 49, 24 |

the new SELENO designations, but supplement them (as secondary designations/synonyms) with the names previously used by the community. Once the new nomenclature is consistently used, the old designations will no longer be needed. We hope that other researchers in the field will join us in implementing this new nomenclature.

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Vadim N. Gladyshev, Elias S. Arnér, Marla J. Berry, Regina Brigelius-Flohé, Elspeth A. Bruford, Raymond F. Burk, Bradley A. Carlson, Sergi Castellano, Laurent Chavatte, Marcus Conrad, Paul R. Copeland, Alan M. Diamond, Donna M. Driscoll, Ana Ferreiro, Leopold Flohé, Fiona R. Green, Roderic Guigó, Diane E. Handy, Dolph L. Hatfield, John Hesketh, Peter R. Hoffmann, Arne Holmgren, Robert J. Hondal, Michael T. Howard, Kaixun Huang, Hwa-Young Kim, Ick Young Kim, Josef Köhrle, Alain Krol, Gregory V. Kryukov, Byeong Jae Lee, Byung Cheon Lee, Xin Gen Lei, Qiong Liu, Alain Lescure, Alexei V. Lobanov, Joseph Loscalzo, Matilde Maiorino, Marco Mariotti, K. Sandeep Prabhu, Margaret P. Rayman, Sharon Rozovsky, Gustavo Salinas, Edward E. Schmidt, Lutz Schomburg, Ulrich Schweizer, Miljan Simonovic, Roger A. Sunde, Petra A. Tsuji, Susan Tweedie, Fulvio Ursini, Philip D. Whanger and Yan Zhang

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